REMARKS

Claim Amendements

Claims 1 and 31 are currently pending herein.

Rejoinder

Applicants believe that Claims 1 and 31 are in condition for allowance and, therefore, respectfully request that withdrawn Claims 3, 5, 10-16, 18, 32, 40, 42, 95, 99 and 147 be rejoined.

Rejection of Claims 1 and 31 Under requirements of 35 U.S.C. §103(a)

Claims 1 and 31 are rejected under 35 U.S.C. §103(a) as being unpatentable over Kandimalla, Kandimalla and Simmonds.

Applicants respectfully disagree that the cited art teaches or suggests an oligonucleotide comprising the instantly claimed RpG dinucleotide, or the linking of two such oligonucleotides via a non-nucleotidic linker. Furthermore, Applicants disagree with the Office Action's characterization of the cited art and the alleged motivation to combine the cited art to reach the instantly claimed compound.

The cited art fails to teach or suggest the instantly claimed oligonucleotide. The Office Action states that one skilled in the art would be motivated to try substituting a bicyclic non-natural cytosine analog as taught by Kandimalla (2001 and '757) with a bicyclic non-natural cytosine analog having the structure shown in Figure 24 as taught by Simmonds because both the bicyclic P-base analog (Kandimalla (2001) Figure 2 and Kandimalla ('757) Figure 28) and the bicyclic cytosine analog 2-oxo-7-deaza-8-methylpurine (Simmonds) share the oxygen and nitrogen hydrogen bond acceptor atoms and nitrogen hydrogen bond donor atom on the same face so as to establish hydrogen bonding with another surface in the same manner as cytosine. Thus according to the Office Action:

It would have been obvious to try substituting a bicyclic non-natural cytosine analog as taught by Kandimalla et al (2001, '757) with a bicyclic non-natural cytosine analog having the structure shown in Figure 24 (Simmonds et al) with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention, and "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipate success, it is likely that product not of innovation but of ordinary skill and common sense." Kandimalla et al ('757) disclose that a bicyclic cytosine analog may be used together with a guanosine analog, i.e. 2'-deoxy-7-deazaguanosine, to yield an immunostimulatory oligonucleotide.

However, although the Office Action goes on at length regarding the supposed similarities between the claimed elements and what is known in the prior art to try to support the rejection, the Office Action fails to explain how one skilled in the art would either be motivated to try, or have a reasonable expectation of success with this "simple" substitution considering Kandimalla (2001) teaches that a YpG-containing oligonucleotide in which Y was deoxy-P-base nucleoside showed **little or no immunostimulatory activity** (see page 809, column 2, lines 22-24)(emphasis added). Thus, According to Office Action's logic, if deoxy-P-base didn't work then common sense would suggest that the instantly claimed R would not work. However, it did. Therefore, not only is the use of the instantly claimed RpG dinucleotide not obvious in view of the prior art, the fact that the instantly claimed compound generated an immune response is a surprising result.

The Office Action continues to wrongly examine the claimed compounds as an "oligonucleotides" in the traditional sense of the term. These compounds do not encode a messenger RNA or a protein. These compounds are not used as probes, primers or antisense oligonucleotides. They do not interact with its target through the well understood mechanism of Watson-Crick base-pairing. Rather, these compounds are ligands for a Toll like receptor (e.g., TLR9), acting through mechanisms which are not well understood, and are novel chemical entities comprising multiple "R" groups. In the absence of a well-understood mechanism, the effect of altering a particular R group in a key portion of the molecule cannot be predicted.

Thus, the claimed compound cannot be treated like "oligonucleotides" as previously understood, but rather as novel chemical entities.

Kandimalla ('757) and Simmonds et al. fail to provide the teachings that Kandimalla (2001) lack. In fact, Kandimalla ('757) is mischaracterized by the Office Action in several locations. First, the Office Action provides an incorrect reading of a quote from pg 5, lines 7-11 of Kandimalla ('757). Kandimalla ('757) teaches that **positional modifications** in the immunostimulatory domain and/or the potentiation domain enhance the immunostimulatory effect in a reproducible and predictable manner. The Office Action suggests that this statement would thereby render any particular chemical modification, at any position within the oligonucleotide, obvious as well. However, a fair reading of Kandimalla ('757) does not go this far. Although Kandimalla ('757) describes the positional modifications of CG-containing oligonucleotides and that many of these compounds elicit a general enhanced or reduced immune response; it is only the enhanced or reduced immune response that is reproducible based on the position modification. However, at the level of each specific immunomer, the different modifications and combinations thereof result in compounds that, although many of which are immunostimulatory and elicit many of the same cytokines, they each elicit the particular cytokines to different degrees, thereby creating a unique immune response profile. This is important because even a slight of degree change in the elicitation of one or more cytokines can have significant physiological effects.

The Office Action goes on to incorrectly state that Kandimalla ('757) teaches two oligonucleotides linked at their 3' ends or internucleoside linkages or a functionalized nucleobase or sugar to a non-nucleotidic linker. Nowhere is the language cited by the Office Action found in Kandimalla ('757). Kandimalla ('757) describes various carbohydrate backbone modifications that can be used as immunostimulatory moieties in the positional modification of a CG-containing oligonucleotide. Kandimalla ('757) also describes the direct 3'-3', 5'-3', 3'-5' and 5'-5' linkages of two oligonucleotides (see Figures 5-10 and Figure 17). However, the compounds of Kandimalla ('757) are structurally different compounds from the instantly claimed compounds. One skilled in the art, based on the teachings of Kandimalla ('757) would not have been motivated to create the instantly claimed structure.

The Office Action then turns to Simmonds to provide the teaching for the specifically claimed analogs illustrated in Figure 24 of the specification. Simmonds describes various base

analogs and states that these analogs may be incorporated into nucleic acids and oligonucleotides. Simmonds goes on to state that these analogs have potential for base pairing with more than one native base or base analog. However, Simmonds use of base analogs that can still form base pairs through Watson-Crick base pairing is meaningless in the field of the instant application. Simmonds provides no teaching or suggestion regarding the effect that the describe base analogs would have on the immunostimulatory properties of a CG-containing oligonucleotide, much less the effect these bases would have if incorporated into the CG dinucleotide.

As the cited art fails to teach or suggests an oligonucleotide comprising the instantly claimed RpG dinucleotide, or the linking of two such oligonucleotides via a non-nucleotidic linker, reconsideration and withdrawal of the rejection is respectfully requested.

Provisional obviousness-type double patenting

Claims 1 and 31 are provisionally rejected over various claims of copending Application Nos. 10/361,111; 10/865,245; 10/925,873; 11/153,054; and 11/174,002.

As stated by the Examiner, this is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Please note that, with regards to patent term, U.S. Application Nos. 10/361,111; 10/865,245; 10/925,873; 11/153,054; and 11/174,002 are the later filed applications.

Therefore, if this provisional double patenting rejection is the only remaining rejection in the application, Applicants request that the Examiner withdraw the rejection in the instant [earlier filed] application thereby permitting this application to issue without need of a terminal disclaimer. (See MPEP §804(I)(B)). Applicants will then consider filing a Terminal Disclaimer or take any other action deemed necessary in the later filed, copending applications.

Claims 1 and 31 are provisionally rejected over various claims of copending Application Nos. 10/694,383 and 10/694,586.

Applicants respectfully disagree. As stated above, a YpG-containing oligonucleotide in which Y was deoxy-P-base nucleoside showed **little or no immunostimulatory activity**. Thus, not only is the use of the instantly claimed RpG dinucleotide not obvious in view of the prior art,

the fact that the instantly claimed compound generated an immune response is a surprising result. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 1 and 31 are provisionally rejected over various claims of U.S. Patent No. 7,276,489.

Applicants respectfully disagree. As stated above, a YpG-containing oligonucleotide in which Y was deoxy-P-base nucleoside showed **little or no immunostimulatory activity**. Thus, not only is the use of the instantly claimed RpG dinucleotide not obvious in view of the prior art, the fact that the instantly claimed compound generated an immune response is a surprising result. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

Dated: August 21, 2008

By: /Joseph C. Zucchero/

Joseph C. Zucchero
Registration No. 55,762

Keown & Zucchero, LLP
500 West Cummings Park Suite 1200
Woburn, MA 01801
Telephone: 781-938-1805
Facsimile: 781-938-4777